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Craniofrontonasal Syndrome: Study of 41 Patients

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Of 41 patients with craniofrontonasal syndrome, 35 were female and 6 were male. Although most cases were sporadic, 7 familial instances were found. Craniofrontonasal syndrome represents a unique, incompletely understood X-linked disorder. Unusual manifestations in females included thick, wiry, and curly hair (49%), anterior cranium bifidum (6%), axillary pterygia (9%), unilateral breast hypoplasia (postpubertal; 11%), and asymmetric lower limb shortness (14%).

KEY WORDS: craniosynostosis, asymmetry, X-linked inheritance

INTRODUCTION

Craniofrontonasal syndrome (CFNS) was identified as a subpopulation of frontonasal "dysplasia" patients by Cohen [1979], who also coined the term CFND. The condition was reported earlier by Reich et al. [1977] and at the same time as Cohen [1979] by Slover and Sujansky [1979]. CFND has been reviewed elsewhere by Cohen [1986], Young [1987], Grutzner and Gorlin [1988], and Gorlin et al. [1990]. Here, we report on our experience with 41 patients.

MATERIALS AND METHODS

From 1979 to 1993, 41 patients with CFNS were studied in the Genetics Department of the Dr. Manuel Gea González General Hospital in Mexico City. Family history, pedigree, maternal history, craniofacial anthropometry, photographs, complete physical examination, full skeletal radiographs, and high resolution chromosome banding studies were carried out on all patients.

RESULTS

Of 41 patients, 35 were female and 6 were male. There were 33 index cases (31 females, 2 males). Seven families with affected relatives were found (Fig. 1). Because the clinical manifestations were much less severe in males than in females (Table I), the index cases were females in 5 of the seven affected families. The index cases were males in two instances because one male had unilateral cleft lip-palate, the other cleft palate. With these exceptions, the only consistent manifestations in the 6 affected males were hypertelorism and malocclusion. No male had craniosynostosis and all 6 affected males were familial cases. In the 7 families of affected individuals, 11 were female, 6 were male (Fig. 1).

Female age range was 6 months to 45 years. Of the 35 females, 25 were prepubescent. Male age range was 7 to 27 years. Of the 6 males, 2 were prepubescent. Mean paternal and maternal ages at the time of conception for the 33 index cases were 31.7 and 27.2 years, respectively. There were no instances of consanguinity nor any known exposure to teratogens.

DISCUSSION

Phenotypic Review

Our CFNS sample size is the largest series reported to date. Females making up the majority, with males being fewer in number and tending to be less severely affected, have also been reported in previous reviews [Cohen, 1986; Young, 1987; Grutzner and Gorlin, 1988; Gorlin et al., 1990]. Manifestations in our affected males were confined to the craniofacial region, consisting of hypertelorism in all 6 cases, cleft lip and/or palate in 2, and malocclusion (cross-bite or posterior open-bite) in all 6. We are aware of several severely affected males. One of us (M.M.C.) knows of two such males in the Netherlands. A third affected male, from Australia, is shown in the monograph of David et al. [1982].[1] Natarajan et al. [1993] reported two severely affected brothers.

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[1]The patient shown by David et al. [1982] (p. 24, Fig. 15) is not stated to be male, but correspondence from David et al. to one of us (M.M.C.) indicates that the patient is male.

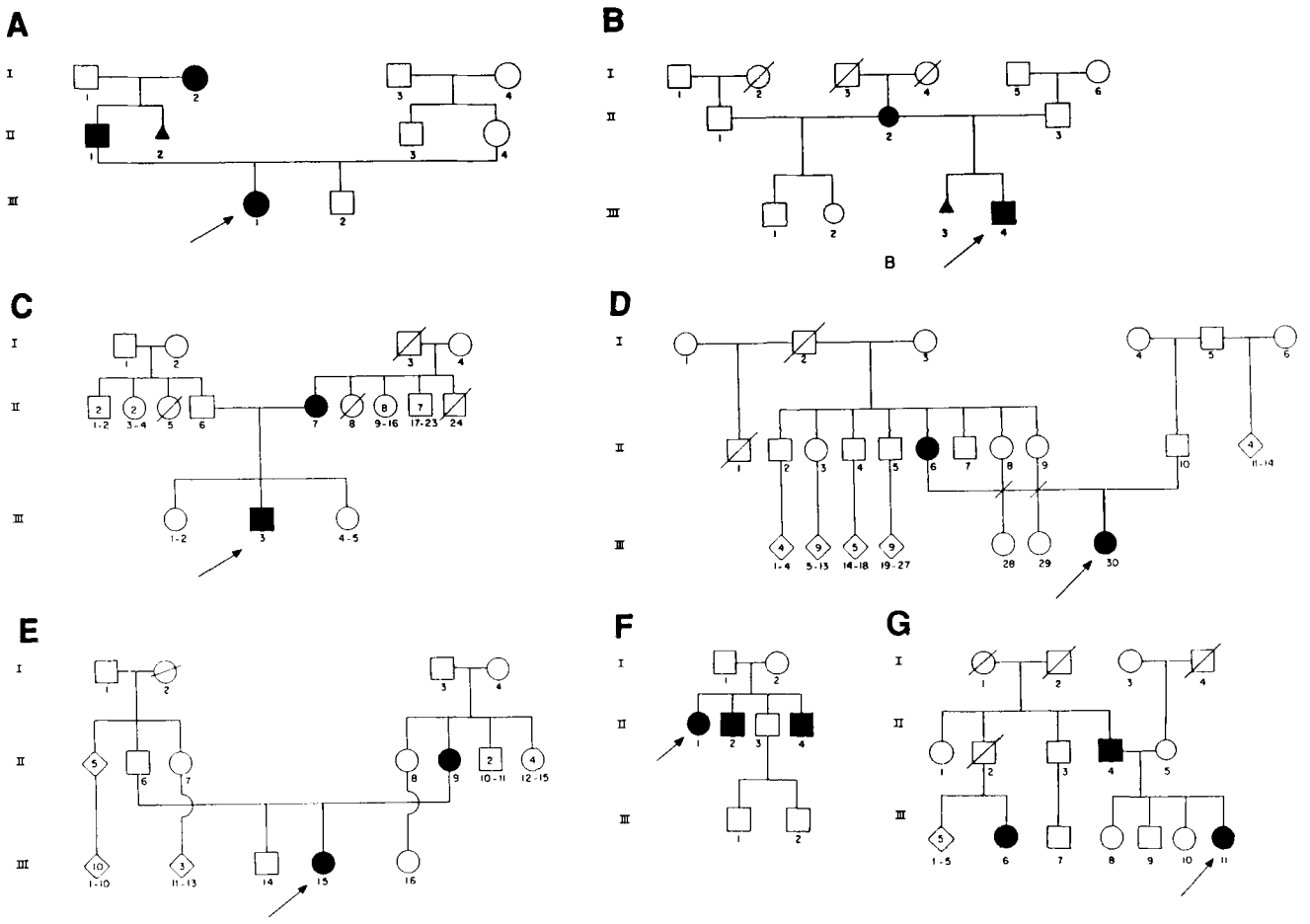

Fig. 1. **A–G:** Seven CFNS families with multipli-affected members.

Although paternal and maternal ages at the time of conception are increased over normal mean values (28.7 and 25.9 years, respectively [Jones et al., 1975]),[2] it is not known whether the increase is significant because normal mean values are drawn from a different population.

Craniosynostosis was present in 94% of our female cases (Table I). Literature review indicates a somewhat higher frequency of CFNS patients without craniosynostosis, particularly in familial instances [Grutzner and Gorlin, 1988; Michels et al., 1989]. Craniofacial asymmetry and asymmetrically placed orbits (both found in 54% of affected females) are related to unicoronal synostosis (also found in 54%; Fig. 2).

Anterior cranium bifidum found commonly in frontonasal "dysplasia" (FD), was found in 6% of our CFNS patients. These were not misdiagnosed FD patients because our patients had the combination of cranium bifidum, *coronal synostosis,* and other manifestations of CFNS (Figs. 3, 4).

Unusual curly hair, frequent in our patients (49% of affected females), has not been emphasized previously except by Hurst and Baraitser [1988] who observed thick wiry hair in all 5 of their cases. In our patients, the curly hair was also thick and wiry and changed into this form between ages 18 and 36 months, in contrast to familial curly hair which has an earlier onset. Furthermore, in our 7 families with CFNS, no unaffected relatives had curly hair. Electron microscopic studies (Fig. 5) showed thicker hair than normal, with irregularities in the disposition and thickness of the keratin filaments.

In 57% of CFNS females, the clavicles were short, S-shaped, downsloping, and forward-directed. Thoracic abnormalities (49% CFNS females) consisted of pectus excavatum or carinatum, thoracic asymmetry, and prominent scapulae.

Unilateral breast hypoplasia (globe size, not areolar size) was observed in 11% of CFNS females (Fig. 6). However, only 10 were postpubescent (≥14 yr) and 4 of them had unilateral breast hypoplasia. Since so many CFNS females were prepubescent, the relatively low overall percentage (11%) reflects age, and unilateral breast hypoplasia, noted previously only by Young [1987], may be a more common manifestation. Unilat-

[2]These normal values are from the U.S. population; no Mexican values have been published.

TABLE I. Manifestations in 41 Patients With Craniofrontonasal Syndrome

	Females (n = 35; %)	Males (n = 6)
Performance		
Normal intelligence	97[a]	6/6
Cranial		
Craniosynostosis	94	0/6
Unicoronal	54	
Bicoronal	17	
Coronal + sagittal	6	
Coronal + metopic	8	
Sagittal	6	
Metopic	3	
Anterior cranium bifidum	6[b]	0/6
Craniofacial		
Craniofacial asymmetry	54	0/6
Thick, wiry, and curly hair	49	0/6
Low anterior hairline	31	0/6
Widow's peak	34	0/6
Hypertelorism	100	6/6
Asymmetrically placed orbits[c]	54	0/6
Strabismus	100	6/6
Short upper facial height (>−3 S.D.)[d]	66	0/6
Bifid nose	66[e]	0/6
Median cleft lip-palate	6	0/6
Unilateral cleft lip-palate	3	1/6
Cleft palate only	11[f]	1/6
Anterior open bite	100	0/6[g]
Short neck with low posterior hairline	17	0/6
Pterygium colli	20	0/6
Skeletal		
Abnormal clavicles[h]	57	0/6
Abnormal thorax[i]	49	0/6
Scoliosis/kyphosis	37	0/6
Cubitus valgus	14	0/6
Asymmetric lower limb shortness	14	0/6
Hands and Feet		
Hyperextensible joints	14	0/6
Mild cutaneous syndactyly	37	0/6
Grooved nails	43	0/6
Clinodactyly, fifth finger	14	0/6
Camptodactyly, usually multiple fingers[j]	37	0/6
Other		
Axillary pterygia	9	0/6
Unilateral breast hypoplasia, postpubertal	11	0/6
Umbilical hernia	9	0/6

[a]One patient was severely retarded.
[b]One patient had frontal meningocele.
[c]With respect to the horizontal axis.
[d]Clinical anthropometric measurement from nasion to incision.
[e]One patient had nasoethmoidal meningocele; another had Tessier No. 13 bony cleft.
[f]One patient had bifid uvula.
[g]All 6 males did have cross-bite or posterior open bite.
[h]Short, S-shaped, downsloping, and forward-directed.
[i]Pectus excavatum or carinatum, thoracic asymmetry, and prominent scapulae.
[j]Mild-to-moderate.

eral lower limb shortness of mild degree (Fig. 6) was observed in 14% of CFNS females, and 4 of the five patients also had unilateral breast hypoplasia (Fig. 6) on the ipsilateral side. Axillary pterygia, found in 9% of our CFNS females, were also reported by Michels et al. [1989].

Fig. 2. Craniofacial asymmetry.

Causal Genesis

Although most cases are sporadic and occur in females who are generally more severely affected than the few reported males, pedigrees showing vertical transmission have been recorded [Cohen, 1979; Slover and Sujansky, 1979; Hunter and Rudd, 1977, see their Fig. 1, pedigree 1; Pruzansky, 1977; Pruzansky et al., 1982; Reynolds et al., 1982; Reich et al., 1985; Kumar et al., 1986; Sax and Flannery, 1986; Šršeň and Prispevok, 1986; Grutzner and Gorlin, 1988; Hurst and Baraitser,1988; Michels et al., 1989; Kere et al., 1990; our series]. Male-to-male transmission has not been ob-

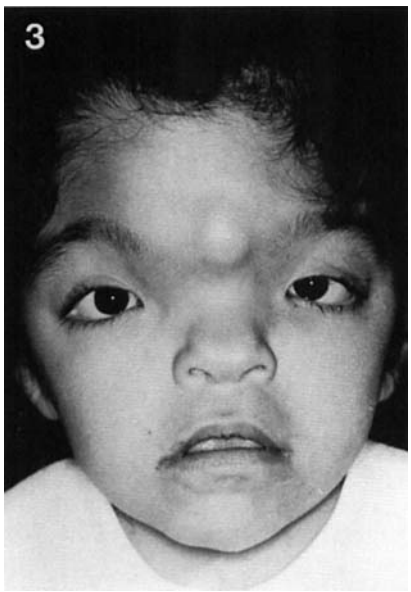

Fig. 3. Girl with CFNS and anterior cranium bifidum.

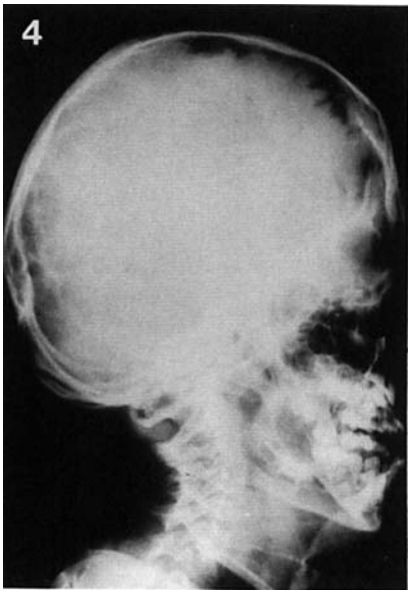

Fig. 4. Radiograph of girl with CFNS shown in Figure 3. Note coronal synostosis.

served in any publications to date, although Reich et al. [1985] noted two instances in an abstract which has yet to appear as a documented publication. Many suggestions have been put forth including X-linked dominant inheritance [Slover and Sujansky, 1979; Pruzansky et al., 1982; Reynolds et al., 1982], metabolic interference [Rollnick et al., 1981], and a semilethal mutation with similarities to the T-locus in the mouse [Sax et al., 1984]. In our opinion, CFNS represents a unique, incompletely understood X-linked disorder. We are aware of two groups attempting to map CFNS, one in the U.S. and one in the U.K.

Differential Diagnosis

CFNS can be distinguished from FD. The female patient with presumed FD and Klippel-Feil anomaly reported by Fragoso et al. [1982] probably had CFNS. The patient reported by Reardon et al. [1990] with craniosynostosis and Poland anomaly is similar to the patient of Webster and Deming [1950][3] and, as suggested by Reardon et al. [1990], probably had CFNS.

The proband reported by Kwee and Lindhout [1983] as an example of CFNS probably had Greig cephalopolysyndactyly. Since the latter syndrome has autosomal dominant inheritance, the severely affected male, presumed to have CFNS by Kwee and Lindhout [1983, 1988] and seconded by Young and Moore [1984], cannot be used as evidence for autosomal dominant inheritance of CFNS.

The family with 3 affected males and 2 affected females reported by Morris et al. [1987] as having CFNS probably represents another disorder. In their family, of 6 patients, only 1 had craniosynostosis, and affected males had manifestations such as short stature, delayed bone age, shawl scrotum, and hypospadias. Possibly their patients may have had brachycephalofrontonasal dysplasia, a dominantly inherited syndrome described by Teebi et al. [1987] and Stratton [1991].

[3]Similar in most respects except craniosynostosis.

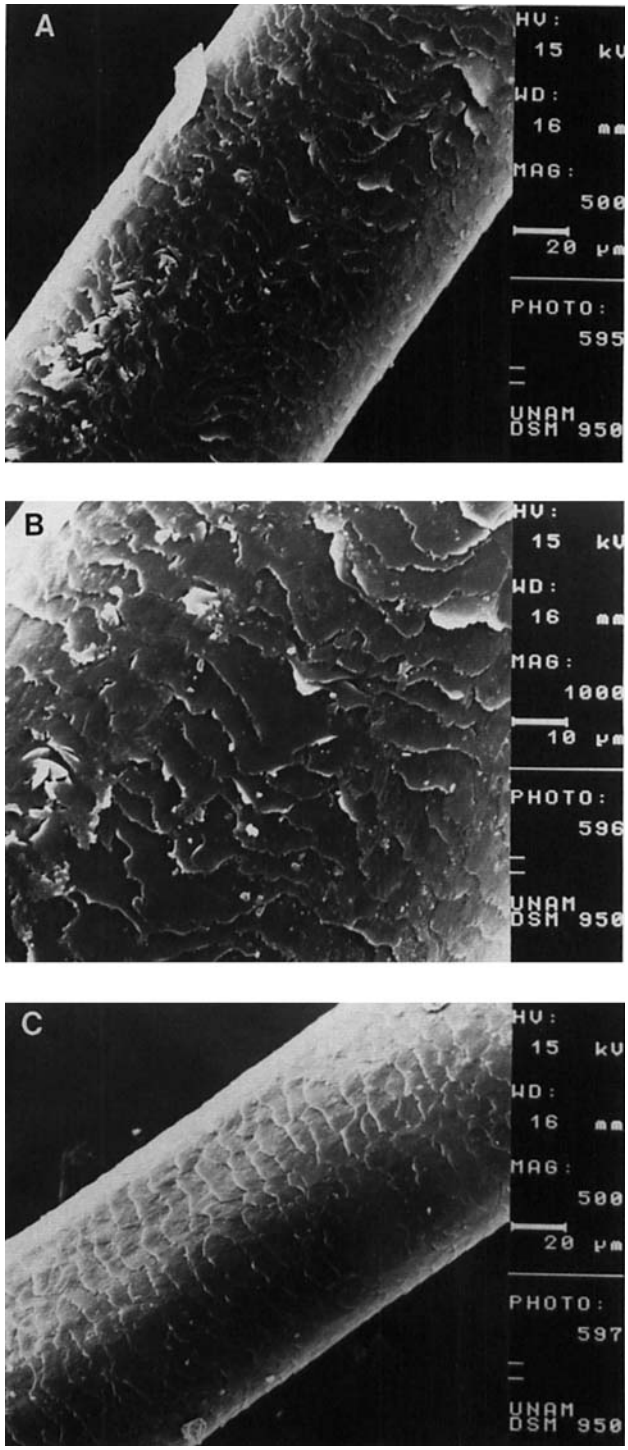

Fig. 5. **A:** Electron micrograph (EM) showing irregularities in disposition of keratin filaments. **B:** EM closeup showing irregular keratin filaments. **C:** EM of normal hair shaft. Note normal disposition of keratin filaments and smaller diameter of hair shaft compared to A.

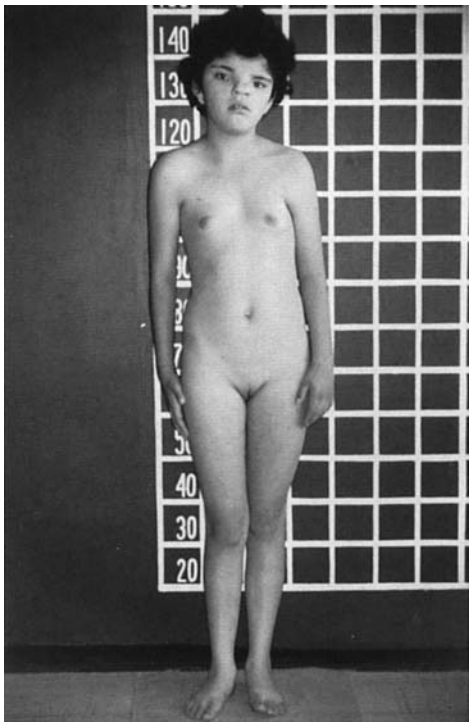

Fig. 6. Unilateral breast hypoplasia (smaller left globe size). Note unilateral shortness of lower limb on ipsilateral side.

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